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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
06/22/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/815,925	BOSSLET ET AL.	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,12 and 15-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 9, 12, 15-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/11/2010 has been entered.

Claims 1-7, 9, 12, 15-18 are pending and currently under consideration.

All previous rejections have been withdrawn in view of Applicants amendments:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 9, 12, 15-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the instant case, claim 1 has been amended to incorporate the following: "wherein the amount of the carbohydrates given as mol monosaccaride/mol fusion protein is 7.04 of mannose, 4.35 of N-acetyl glucosamine, 0.6 of fucose and 0.54 of N-acetylneuraminic acid". However, it is unclear whether said wherein clause is referring to the "total" amount of the carbohydrates present in the carbohydrate complement or alternatively to the exposed carbohydrate residues. As such, there is insufficient antecedent basis since it is unclear which carbohydrates the mol % is referring to.

Assuming that the "wherein" clause is referring to the total amount of carbohydrates present in the carbohydrate complement, A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and

Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 1 recites the broad recitation a carbohydrate complement comprising an exposed terminal carbohydrate mannose residue and at least one exposed terminal carbohydrate residue selected from the group consisting of galactose, N-acetylglucosamine, N-acetyllactose, glucose, N-acetylneuraminic acid and fucose, and the claim also recites " wherein the amount of the carbohydrates given as mol monosaccaride/mol fusion protein is 7.04 of mannose, 4.35 of N-acetyl glucosamine, 0.6 of fucose and 0.54 of N-acetylneuraminic acid" which is the narrower statement of the range/limitation. In other words, the first section describing the makeup of the carbohydrate complement allows for the incorporation of galactose, N-acetylglucosamine, N-acetyllactose, glucose, N-acetylneuraminic acid and fucose. However, the narrower limitation which specifically defines the amount of the carbohydrates present does not include galactose, N-acetyllactose or glucose. As such, the claims describe a carbohydrate complement broadly, but than specifically identifies the components of the carbohydrate complement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 9, 12, 15-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. THIS IS A NEW MATTER REJECTION.

In the instant case, claim 1 is drawn to a compound comprising a bifunctional fusion glycoprotein or bifunctional glycoprotein conjugate, the compound comprising a carbohydrate complement, and: a) at least one first portion which possesses enzymatic activity, b) at least one second portion which binds specifically to an epitope of a tumor-specific antigen, wherein the bifunctional fusion glycoprotein has been synthesized in CHO cells. Claim 1 has been amended to include the limitation "wherein the amount of the carbohydrates given as mol monosaccaride/mol fusion protein is 7.04 of mannose, 4.35 of N-acetyl glucosamine, 0.6 of fucose and 0.54 of N-acetylneuraminic acid". However, while the specification clearly provides support for this limitation for a specific humanized two chain fusion protein expressed in CHO cells (see for example, page 19, lines 10-29 including Table 1a), the limitation has no clear support in the specification and the claims as originally filed for the broad genus which Applicants are claiming. As such, Applicant is required to cancel the new matter in the response to this Office Action. Alternatively, applicant is invited to provide sufficient written support for the "limitation" indicated above. See MPEP 714.02 and 2163.06

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-7, 9, 12 and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seemann (Canadian Patent Application 2,062,047; laid open to the public on 8/29/1992, of record) in view of Page (US Patent No. 5,545,405, 1991), Mattes (U.S. Patent 4,859,449; issued 08/1989, of record) or Winkelhake (Winkelhake, J. Biological Chemistry, 251(4): 1074-1080, 1976, of record) or Day et al .(Journal of Biological Chemistry 1980; 255: 2360-2365).

Seemann teaches a fusion protein comprising the general formula huTuMAb-L–β-gluc, wherein huTuMA is a humanized tumor-specific moloclonal antibody or fragment thereof , L is a linker and β-gluc comprises human β-glucuronidase (page 1, 1st paragraph). With regards to huTuMAb, Seemann et al. teach that the huTuMAb includes the antibody binding fragments of anti-CEA BW431/26 monoclonal antibody (page 3, lines 16-23; page 17, lines 25+; and page 23, *Example O*). With regards to the fusion protein, Seemann et al. teach that the fusion protein is synthesized in BHK cells (page 10, Example I). Moreover, Seemann et al. teach the fusion proteins can be further modified in order to achieve an increased half-life, wherein the fusion proteins are treated with an oxidizing agent which cleaves the carbohydrate ring, e.g. chemical degradation, which can be further derivatized by reductive animation which generates a new carbohydrate residue (page 4, lines 12-30). Seeman et al. further teach a pharmaceutical composition comprising the fusion protein, wherein the fusion protein was dissolved in tris/HCl buffer (*page 25, Example Q*).

Seemann does not explicitly teach that the fusion protein is synthesized in CHO cells. Nor does Seeman explicitly teach that the fusion proteins or conjugates comprise an exposed galactose, mannose, N-acetylglucosamine, lactose, N-acetyllactose, glucose or fucose.

Page teaches the use of CHO cells for the production of antibodies (col. 2, line 51 to col. 6, line 26). In particular, Page et al. teaches that CHO cells enables the balanced expression of light and heavy chans and that balanced expression is desirable give that the light and heavy chains are linked together in the antibody molecule in equimolar proportions (see col. 2, lines 62-66).

Mattes teaches chemical methods for addition of galactose or glucose to an anti-CEA antibody for increased clearance (col. 7, lines 6-col. 8, line 8). Mattes further teaches enzymatic methods of carbohydrate degradation (col. 6, lines 47-64). Moreover, Mattes teaches the desirability of increased clearance of therapeutic antibodies from the blood for the purpose of reducing side effects of antibodies or antibody conjugates caused by the presence of the antibody or antibody conjugate in the circulation.

Winkelhake teaches methods of enzymatic degradation (page 1075, 2nd col.).

Day et al .teach that the exposure of galactose, mannose, N-acetylhexosamine or fucose residues on glycoproteins results in their rapid clearance from the circulation by carbohydrate specific recognition systems in heptatic and reticuloendothelial tissues (page 2360, 1st column, 1st full paragraph).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the references so as to synthesize the fusion protein taught by Seeman et al. via CHO cells in view of the teachings of Page et al. One would have been motivated to do so because CHO cells of Page enable the balanced expression of light and heavy chains and that balanced expression is desirable give that the light and heavy chains are linked together in the antibody molecule in equimolar proportions. As such, one of ordinary skill in the art would have a reasonable expectation of success that by synthesizing the fusion protein taught by Seeman et al. via CHO cells in view of the teachings of Page et al., one would achieve a fusion protein comprising an antibody having balanced expression of light and heavy chains.

Moreover, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the references so as to modify the fusion protein taught by Seemann with a mannose, as well as galactose or glucose in view of the teachings of Mattes, Winkelhake or Day et al because both Mattes and Day teach the increased clearance of modified antibodies is via the Ashwell receptors (asialoglycoprotein receptors) in the liver that recognize sugars such as galactose or mannose. Thus, it is well known in the art to modify antibodies by either adding a sugar such as galactose by chemical means or by enzymatically degrading sialated carbohydrate groups using enzymes such as neuraminidase to expose sugars such as galactose. As such, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the fusion protein taught by Seemann with a mannose, as well as a galactose or glucose in view of the teachings of Mattes, Winkelhake or Day, one would achieve a fusion protein having increased clearance from the circulation.

Note: In order to expedite prosecution, the Examiner would like to respond to Applicants arguments as they relate to the present invention. In response to the previous rejection, Applicants assert that the combination (previous) does not teach or suggest the present claims. In particular, Applicants assert that the prior art does not teach or suggest the limitation "wherein the amount of

the carbohydrates given as mol monosaccaride/mol fusion protein is 7.04 of mannose, 4.35 of N-acetyl glucosamine, 0.6 of fucose and 0.54 of N-acetylneuraminic acid". In response to these arguments, the Examiner acknowledges and does not dispute this assertion. However, in view of the 112 2nd rejections set forth above, the Examiner recognizes that broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. As such, the rejection has been applied broadly, e.g., wherein the carbohydrate complement comprises an exposed terminal carboxylate mannose residue and at least one exposed terminal carbohydrate such as galactose which is not required by the narrower limitation.

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Seemann (Canadian Patent Application 2,062,047; laid open to the public on 8/29/1992, of record) in view of Page (US Patent No. 5,545,405, 1991), Mattes (U.S. Patent 4,859,449; issued 08/1989, of record) or Winkelhake (Winkelhake, J. Biological Chemistry, 251(4): 1074-1080, 1976, of record) or Day et al .(Journal of Biological Chemistry 1980 and further in view of Bosslet (Bosslet et al, Br. J. Cancer 65: 234-238, 1992) and Jahde (Jahde et al, Cancer Res. 52: 6209, 1992;).

Seemann in view of Page and Mattes or Winkelhake or Day teach, as applied to claims 1-7, 9, 12 and 15-16, a pharmaceutical composition comprising a recombinantly made fusion glycoprotein comprising the antigen binding fragment of the monoclonal antibody BW431/26 linked to a β-glururonidase having an exposed galactose residue and a pharmaceutically acceptable carrier such as Tris/HCl buffer..

Seemann in view of Page and Mattes or Winkelhake or Day do not explicitly teach that the pharmaceutical composition further comprises an agent that lowers the intracellular pH of tumor cells.

Bosslet teaches that that activity of β-glucuronidase increases at a pH that is lower than physiological pH (page 236, 2nd col.).

Jahde teaches methods of lowering intracellular pH of tumors comprising administering glucose (page 6210, 2nd column, *Results*).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the references so as to modify the pharmaceutical composition as taught by Seemann in view of Mattes or Winkelhake or Day to include an agent that lowers the intracellular pH of a tumor in view of Bosslet and Jahde. One would have bee motivated to do so because Bosslet teaches that the activity of β-glucoronidase increases at a pH that is lower that physiological pH and Jahde provides agents which are capable of reducing intracellular pH. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifing the pharmaceutical composition as taught by Seemann in view of Mattes or Winkelhake or Day to include an agent that lowers the intracellular pH of a tumor in view of Bosslet and Jahde, one would achieve a pharmaceutical composition having an agent which increases the enzymatic activity of β-glucuronidase.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Seemann (Canadian Patent Application 2,062,047; laid open to the public on 8/29/1992, of record) in view of Page (US Patent No. 5,545,405, 1991) and Mattes (U.S. Patent 4,859,449; issued 08/1989, of record) or Winkelhake (Winkelhake, J. Biological Chemistry, 251(4): 1074-1080, 1976, of record) or Day et al .(Journal of Biological Chemistry 1980) and further in view of Bagshawe (U.S. Patent 5,632,990; issued 05/1997; filed 12/1990).

Seemann in view of Page and Mattes or Winkelhake or Day teach, as applied to claims 1-7, 9, 12 and 15-16 above, a pharmaceutical composition comprising a recombinantly made fusion glycoprotein comprising the antigen binding fragment of the monoclonal antibody BW431/26 linked to a β-glururonidase having an exposed galactose residue and a pharmaceutically acceptable carrier such as Tris/HCl buffer.

Seemann in view of Page and Mattes or Winkelhake or Day do not explicitly teach that the pharmaceutical composition further comprises galactose.

Bagshawe teaches the use of galactosylated antibody constructs for the purpose of increased clearance and further teaches methods that comprise the additional use of a substance for blocking glactose residues for the purpose of maintaining a high level of conjugate in the plasma until the galactose receptors are again free to take up the galactosylated conjugate. Bagshawe teaches that

asialofetuin binds strongly to galactose receptors but that less immunogenic substances may be identified col. 4, lines 33-41).

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the references so as to modify the pharmaceutical composition as taught by Seemann in view of Mattes or Winkelhake or Day to include galactose for the purpose of temporarily decreasing clearance of the fusion glycoproteins or conjugates in view of the teachings of Bagshawe et al.. One would have been motivated to do so because Bagshawe et al. teach the addition of a second substance to block galactose receptors from binding with the galactosylated conjugate. Thus, one of ordinary skill in the art would have had a reasonable expectation of success in using galactose as a substance for temporarily decreasing clearance of the fusion glycoproteins or conjugates because the receptors are galactose receptors.

Therefore, NO claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf

Primary Examiner
Art Unit 1642

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